REMARKS

I. Status of the Claims

Claims 1 through 5 and 7 through 9 are pending in the application. Reconsideration of the outstanding rejections is respectfully requested in view of the foregoing amendment and these remarks.

II. Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 7 through 9 under 35 U.S.C. § 112, first paragraph is moot in view of the amendment to claim 7 deleting reference to "prevention" of osteoporosis and deleting from claim 8, "prevention" of skin, epithelial or mucosal atrophy. Applicants submit that the present claims are directed to a method for improving the bioavailability of a compound.

Claim 1 has been amended to incorporate the limitations of claim 6, to clarify that "food intake" means administering a foodstuff having nutritional value that causes secretion of bile acids. This clarifies the mechanism of the claimed food effect, and should clarify that water, or other active drug compounds, are not considered "food" for the purposes of the present claims.

III. Rejections Under 35 U.S.C. § 103

Claims 1 through 9 have been rejected over D.M. Biskobing, *Expert Opinion Invest. Drug* (2003) 12(4) ("Biskobing") in view of WO 97/32574 ("Harkonen") and U.S. Patent No. 6,245,819 ("Halonen").

Before turning to the specifics of the rejection, Applicants believe it is worthwhile to make certain basic observations about the "food effect" phenomenon and bioavailability. In general, it is well known, that food typically slows the action of a drug.

Thus, a well known text in this field, Rowland M. Tozer, Clinical Pharmacokinetics - Concepts and Applications, 3rd Ed. Williams & Wilkins, 1995, explains at page 121: "[f]ood, especially fat, slows gastric emptying, which explains why drugs are frequently recommended to be taken on an empty stomach when a rapid onset of action is desired." Further, on the same page, "slowing gastric emptying slows the rate of absorption of acetaminophen, as seen by a decrease in the maximum plasma concentration and a longer time to reach this concentration."

This general phenomenon cited is in contrast to the inventors' finding, set forth in the claims, that the more fat a meal contained the more it enhanced the absorption of ospemifene, leading to higher maximal concentrations in plasma. These increases in plasma concentration are clinically meaningful, corresponding to plasma levels obtained when ospemifene is administered in dosages three times as large, without food.

Without wishing to be bound by theory, it is believed that the mechanism of absorption enhancement is related to the biliary secretion induced by the meal since this enhancement of absorption can be replicated also in animals with fatty vehicles. The fatty contents of the meal are critical to stimulate biliary excretion (*i.e.*, bile acids). Thus, the claim as amended, requiring secretion of bile acids, more closely reflects the novel discovery represented herein.

The important element of the present claims that is not disclosed in any of the references is the use of food to increase the bioavailability of ospemifene. This result is entirely unexpected, and particularly surprising in view of the fact that toremifine, which is a close analog of ospemifene, does not demonstrate increased bioavailability taken with food.

Harkonen says at page 3, lines 9-10: "The compounds of the invention may be administered alone or together with other active compounds." This appears to be the sole reference to "other active compounds." There is no disclosure of taking the compound (ospemifene) with food, no disclosure of increasing the bioavailability of ospemifene with food, and no disclosure of using any "other active compounds" to increase bioavailability, of ospemifene or any other drug.

As noted in the specification at page 2, a study on the bioavailability of toremifene, M. Antilla, *European Jrnl. Cancer*, 1997 V. 33, Supp. 8, 1144, showed that a close analog of ospemifene did not increase bioavailability when taken with food. Furthermore, the improved bioavailability of ospemifene taken with food was not earlier achieved in rats, not even using solubles as vehicle. The food interaction is thus not an obvious or inherent feature of ospemifene, as the result can be verified only when the compound is studied clinically. This applies even more to the strength of the effect, which was found to be surprisingly good. Therefore, the expectation in the art would have been that administration with food would not increase the bioavailability of ospemifene.

The Office Action asserts at pages 4-5 that "[m]ost drugs are taken with food in order to prevent patient from feeling nausea, vomiting or any other symptom related with taken drugs on an empty stomach." Even if true, this would not render obvious the claimed subject matter, because the cited references do not teach or suggest the increased bioavailability of ospemifene as a result of administering the compound with food.

The "familydoctor.org" reference cited by the Examiner also shows that the interaction of drugs with food is not uniform. Therefore, the increased bioavailability of

ospemifene when administered with food is not expected or obvious in light of this additional reference.

Indeed, the person of ordinary skill in the art would be well aware that food effects are highly variable from drug to drug. The FDA provides guidance in this regard, noting that food can change the bioavailability of a drug and can influence the bioequivalence between test and reference products, with clinically significant consequences, stating: "In practice, it is difficult to determine the exact mechanism by which food changes the BA [bioavailability] of a drug product without performing specific mechanistic studies." (FDA Guidance, 2002). Therefore, the expectation in the prior art generally, is that food would not increase the bioavailability of ospemifene. Moreover, no comparable effect was noted with the structurally similar toremifene, which further indicates that the result is unexpected and non-obvious.

For the foregoing reasons, the cited prior art does not make obvious a method of increasing the bioavailability of ospemifene by administering the compound with food.

IV. Obviousness-Type Double Patenting

All of the claims have been rejected for alleged obviousness-type double patenting over U.S. Applications Nos. 10/783,092, 11/183,185, and 11/201,098, and over U.S. Patent No. 6,984,665. These rejections are respectfully traversed, as none of the applications applied in the rejections, or the patent, contain any disclosure whatsoever relating to enhancing bioavailability.

The following statement at page 6 of the Office Action is incorrect both as to the facts and the law:

> *In response, this found unpersuasive, because this is an obviousness double patenting, does not need to have every single disclosure. The scope as a whole is the same. Administering the drug with or without food is not going to change the mechanism of action of the drug in the system, once the drug gets in the system it is available.*

First, the "scope as a whole" of the claims is not the same. Administration of ospemifene according to the claims of the '665 patent, for example, if it was done without food, would not infringe the present claims. Accordingly, as the claims cover different inventions, they do not have the same "scope as a whole."

Further, while it may not be necessary for the obviousness-type double patenting "reference" to disclose every feature of the rejected claims, at a minimum the differences have to be obvious to one of ordinary skill in the art. *See*, *e.g.*, *In re Lonardo*, 119 F.3d 960 (Fed. Cir. 1997). As demonstrated above, that is not the case here, where the food effect is neither obvious nor expected in view of the prior art.

It is also misleading to suggest that, "once the drug gets in the system it is available." An important element of the present claims is that the mechanism by which ospemifene "gets into the system" impacts how effective the drug is. It is well known that the affinity with which a drug binds with its carrier system can have a significant impact on the free drug fraction available for absorption, distribution, metabolism and excretion and can therefore play a major role in defining drug pharmokinetics and therapy. *See*, *e.g.*, *J. Receptor & Signal Transduction Research*, 21 (2&3) 215-257 (2001). The present claims require administration with food so that bioavailability is increased. Accordingly, increasing bioavailability by administration with food is an additional claim element to be considered, and not dismissed out of hand, as has been done in the Office Action.

The '092 application does not disclose the administration of food to enhance the bioavailability of ospemifene, and the '092 application claims require treatment of a subject suffering from "increased bone turnover." Therefore, the scope of the '092 patent claims is not at all the same as the scope of the present claims. Applicants submit that an obviousness-type double patenting rejection is inappropriate.

The co-pending '185 application also does not disclose administration of ospemifene with food to enhance the bioavailability of the drug and, moreover, the '185 application is directed to treating androgen deficiency in males. The claims have completely different scope, and an obviousness-type double patenting rejection is improper.

Likewise, the present claims are not obvious in view of the '665 patent claims or the (related) '098 application, at least because the increased bioavailability achieved by taking ospemifene with food would not have been obvious.

CONCLUSION

For at least the foregoing reasons, applicants submit that the claims as amended are allowable and respectfully request that the application be passed to issue

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

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